Remarks

Claims 50-92 are pending in the application. Claims 55-58, 64-67, 69-75, 81-84, and 86-92 stand withdrawn from consideration pending rejoinder. Claims 50-54, 59-63, 68, 76-80 and 85-88 stand rejected.

The present invention, as set forth in claim 50, is directed to a method of in-vivo localizing a substantially water-insoluble drug within the extracellular space of solid tumor tissue in an animal. The method comprises administering a water-soluble prodrug to the animal, wherein the prodrug comprises the drug substituted with a prosthetic group that is cleavable by an enzyme, which is present in the extracellular space of the tumor and which is produced naturally by cells of the tumor. The enzyme is unique to tumor cells or is produced at concentrations that are higher than that in normal tissues. Cleavage of the prosthetic group from the prodrug yields the substantially water-insoluble drug entrapped in the extracellular space, wherein the entrapped drug has a radionuclide or a boron cage.

Claims 50-53, 59-63 and 68 are rejected under 35 U.S.C. §103(a) over Pastan (US 5,489,525) in view of Haugland (US 5,316,906) and Hansen (US 5,851,527), Lebioda et al. (US 5,763,490), Mertens (US 5,021,220) and Christenson (US 4,107,285).

Pastan discloses monoclonal antibodies which bind to an antigen associated with prostate cells. There is no teaching or suggestion in Pastan for a method of in-vivo localizing a substantially water-insoluble drug within the extracellular space of solid tumor tissue in an animal using a prodrug having a prosthetic group that is cleavable by an enzyme, which is present in the extracellular space of the tumor and which is produced naturally by cells of the tumor.

Haugland is cited to make up for the deficiencies of Pastan. However, Haugland ***fails*** to make up for the deficiencies of Pastan. Haugland discloses fluorescent precipitating substrates made from a class of fluorophores, which include compounds similar to those of the present invention, **except that** there is no teaching or suggestion that the compounds have a radionuclide or a boron cage. Indeed, Haugland specifically teaches substrates for measuring enzyme activity

and that the phenolic products that are specifically formed are nontoxic to cells. There also is no teaching or suggestion in Haugland for a method of in-vivo localizing a substantially water-insoluble drug within the extracellular space of solid tumor tissue in an animal using a prodrug having a prosthetic group that is cleavable by an enzyme, which is present in the extracellular space of the tumor and which is produced naturally by cells of the tumor.

It is not seen how one of ordinary skill in the art would combine the teachings of Hoagland with Pastan to arrive at the present invention. Hoagland teaches a method for measuring enzyme activity of whole organisms or cells without being toxic to the cells. However, Pastan teaches a method for conjugating radioisotopes with antibodies that bind to cancerous prostate cells. Why would one of ordinary skill in the art have combined these teachings? There is nothing in either reference or in there combination that would lead one of ordinary skill in the art to make the combination. Further, even if the combination were made, the combination still would not provide a method of in-vivo localizing a substantially water-insoluble drug within the extracellular space of solid tumor tissue in an animal using a prodrug having a prosthetic group that is cleavable by an enzyme, which is present in the extracellular space of the tumor and which is produced naturally by cells of the tumor, as set forth in claim 50.

Hansen is cited to further make up for the deficiencies in Pastan and Haugland. Hansen discloses a method for antibody targeting of therapeutic agents. Hansen also teaches the use of an antibody-enzyme conjugate. The antibody is conjugated with an exogenous enzyme wherein the antibody selectively binds to a cell site to tether the enzyme at that site. Again, there is no teaching or suggestion for a method of in-vivo localizing a substantially water-insoluble drug within the extracellular space of solid tumor tissue in an animal using a prodrug having a prosthetic group that is cleavable by an enzyme, which is present in the extracellular space of the tumor and which is produced naturally by cells of the tumor, as set forth in claim 50.

It is not seen how one of ordinary skill in the art would have combined the teachings of Hansen with Hoagland and Pastan to arrive at the present invention. None of the references, alone or in combination, teach or suggest a method of in-vivo localizing a substantially water-

insoluble drug within the extracellular space of solid tumor tissue in an animal using a prodrug having a prosthetic group that is cleavable by an enzyme, which is present in the extracellular space of the tumor and which is produced naturally by cells of the tumor, as set forth in claim 50.

Lebioda et al. also is cited to make up for the deficiencies in Pastan, Haugland and Hansen. Lebioda discloses a method of treating prostate cancer by administering tartrate ions to inhibit PAP. However, Lebioda also ***fails*** to teach or suggest a method of in-vivo localizing a substantially water-insoluble drug within the extracellular space of solid tumor tissue in an animal using a prodrug having a prosthetic group that is cleavable by an enzyme, which is present in the extracellular space of the tumor and which is produced naturally by cells of the tumor, as set forth in claim 50.

Thus, it is not seen how one of ordinary skill in the art would have combined the teachings of Lebioda with Hoagland, Hansen and Pastan to arrive at the present invention. None of the references, alone or in combination, teach or suggest a method of in-vivo localizing a substantially water-insoluble drug within the extracellular space of solid tumor tissue in an animal using a prodrug having a prosthetic group that is cleavable by an enzyme, which is present in the extracellular space of the tumor and which is produced naturally by cells of the tumor, as set forth in claim 50.

Next, Mertens is cited to make up for the deficiencies in Pastan, Haugland, Hansen and Lebioda. Mertens discloses kits for preparing radiodiagnostic compositions. Once again, there is no teaching or suggestion for a method of in-vivo localizing a substantially water-insoluble drug within the extracellular space of solid tumor tissue in an animal using a prodrug having a prosthetic group that is cleavable by an enzyme, which is present in the extracellular space of the tumor and which is produced naturally by cells of the tumor, as set forth in claim 50.

It is not seen how one of ordinary skill in the art would have combined the teachings of Mertens with Lebioda, Hoagland, Hansen and Pastan to arrive at the present invention. None of the references, alone or in combination, teach or suggest a method of in-vivo localizing a

substantially water-insoluble drug within the extracellular space of solid tumor tissue in an animal using a prodrug having a prosthetic group that is cleavable by an enzyme, which is present in the extracellular space of the tumor and which is produced naturally by cells of the tumor, as set forth in claim 50.

Finally, Christenson is cited to make up for the deficiencies in Pastan, Haugland, Hansen, Lebioda and Mertens. Christenson discloses radiolabelling of quinazolinone for an immunoassay. Christenson **fails** to make up for the deficiencies of Pastan, Haugland, Hansen, Lebioda and Mertens. Christenson also **fails** to teach or suggest a method of in-vivo localizing a substantially water-insoluble drug within the extracellular space of solid tumor tissue in an animal using a prodrug having a prosthetic group that is cleavable by an enzyme, which is present in the extracellular space of the tumor and which is produced naturally by cells of the tumor, as set forth in claim 50.

Therefore, it is not seen how one of ordinary skill in the art would have combined the teachings of Christenson with Mertens, Lebioda, Hoagland, Hansen and Pastan to arrive at the present invention. None of the references, alone or in combination, teach or suggest a method of in-vivo localizing a substantially water-insoluble drug within the extracellular space of solid tumor tissue in an animal using a prodrug having a prosthetic group that is cleavable by an enzyme, which is present in the extracellular space of the tumor and which is produced naturally by cells of the tumor, as set forth in claim 50.

Claims 54, 76-80 and 85 are rejected under 35 U.S.C. §103(a) over Pastan in view of Haugland and Hansen, Lebioda et al., Mertens and Rose (US 5,816,259). Pastan, Haugland, Hansen, Lebioda et al. and Mertens are discussed above. Rose ***fails*** to make up for the deficiencies in Pastan, Haugland, Hansen, Lebioda et al. and Mertens. Rose also ***fails*** to teach or suggest a method of in-vivo localizing a substantially water-insoluble drug within the extracellular space of solid tumor tissue in an animal using a prodrug having a prosthetic group that is cleavable by an enzyme, which is present in the extracellular space of the tumor and which is produced naturally by cells of the tumor, as set forth in claim 54.

Rose discloses a method for the accumulation of trace-labeled or therapeutic insoluble molecules **in** (i.e., "with**in**") targeted cells of a living host. Accumulation is achieved by administering a reagent having a targeting agent attached to a chemical agent, which binds to antigenic receptors on targeted cells which endocytose the reagent and transport it into the lysosomes where enzymes detach the chemical agent to be **retained in** the cells.

In the presently claimed invention, there is no targeting agent. Surprisingly, the endogenous enzymes produced by the tumor cells through cleavage of the prodrug cause the accumulation of the substantially water-insoluble drug within the extracellular space of solid tumor tissue, i.e., outside the cell, without the aid of a targeting agent as a component of the prodrug. Nothing in the cited references teaches or suggests the presently claimed method.

Thus, it is not seen how the presently claimed invention would have been obvious to one of ordinary skill in the art in view of any combination of the cited references.

In view of the discussion above, it is respectfully submitted that the present application is in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

If upon reconsideration any issues remain, the Examiner is requested to call Applicant's undersigned attorney to discuss the remaining issues. Upon allowance of claims 50 and 54, Applicant requests that all claims dependent from claims 50 and 54 be reinstated and allowed.

Dated: 14 July '06

Respectfully submitted,

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